Developing Biological Therapeutics for Rare Plasma Protein Disorders

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Background

- 1938- birth of modern pharmaceutical industry based on research and development of potent new medicines
  - Requirement to test drugs for safety before marketing
  - No requirement for companies to inform FDA of medical experiments for new drugs before conducting the experiments
  - Physicians could administer drugs, without consent, to unlimited numbers of patients as long as the work was deemed experimental

Regulatory Background

- Guidance for Industry: Clinical Evidence of Effectiveness
  - 1962

    Amendment to the Federal Food, Drug, and Cosmetic Act to add requirement for demonstration of effectiveness of drug and biologic products

  - Prior to 1962, manufacturers required to demonstrate only safety

Evidence of Effectiveness

- Quantity of Evidence Necessary to Support Effectiveness
  - Section 505(d) of FD and C Act
    - *"substantial evidence"*
      - *"evidence consisting of adequate and well controlled investigations…by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could…be concluded…that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling…"*

Evidence of Effectiveness (2)

- Interpreted by FDA to mean that generally two adequate and well-controlled studies, each convincing in its own right, necessary to establish effectiveness

Evidence of Effectiveness (3)

- "On occasion, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens,…in other states of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use."

Evidence of Effectiveness (4)

- "…FDA has relied on only a single adequate and well-controlled efficacy study to support approval- generally only in cases in which a single, multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds."

Evidence of Effectiveness (5)

- FDAMA
  - Section 115(a) amended section 505(d) of the Act
    - FDA may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.”

Evidence of Effectiveness (6)

- PHS Act (Section 351)
  - Licenses for biologics are issued upon showing that the products meet standards designed to ensure “continued safety, purity, and potency…”
    - Potency- specific ability of product, demonstrated in laboratory tests or adequately controlled clinical data, to effect a given result

Evidence of Effectiveness (7)

- Proof of effectiveness consists of controlled investigations as defined in the provision for “adequate and well-controlled studies” for new drugs unless waived as not applicable to the biologic product or not essential to the validity of the study

Evidence of Effectiveness (8)

- 21 CFR 601.25(d)(2)-alternative methods to substantiate effectiveness acceptable for biological products
  - Serological response data = one example “provided that a previously accepted correlation with clinical effectiveness exists”

Evidence of Effectiveness: Scientific Basis

- Unanticipated, undetected, systematic biases
- Inherent variability in biologic systems may result in a finding of efficacy by chance alone
- Results may be driven by outcome from one center
- Scientific fraud

Quantity of Evidence Needed

- "Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study."
  - Mortality, irreversible morbidity, prevention of disease with potentially serious outcome

What Makes a Single Study OK?

- Large, multicenter study in which no one site provides a disproportionate percentage of the subjects
- Consistency across subsets in large trials with relatively broad entry criteria
- Multiple endpoints involving different events
- Statistically very persuasive findings

What Makes One Study OK? (2)

- Caveats
  - Must consider the possibility of an incorrect outcome
  - Available data must be examined for potential to support or undercut the results

How to Get from Good Idea to Market

- Phases of Study
  - Pre-IND
  - IND (Investigational New Drug Application)
    - Phase I
    - Phase II
    - Phase III
  - BLA (Biological License Application
  - Licensure
    - Phase IV (Post-marketing)

Clinical Trials

- "A prospective study comparing the effects of intervention(s) against a control in human beings."
  - Freeman, Furberg, Demets, 1995
- "The purpose is to distinguish the effect of the drug form other influences, such as spontaneous change… placebo effect, or biased observation."
  - 21 CFR 314.126

Concept of Clinical Trial

- Assess efficacy by comparing outcomes in group receiving the drug with controls
- Try to isolate receipt or non-receipt of the drug as the only important difference between groups
- Gold standard is randomized well-controlled trial where balance is ensured by the randomization process.

Study Participants

- Phase I- risk/benefit
  - Normal volunteers- may have no benefit
  - Patients for whom agent is intended, may have more advanced disease than intended population
- Later phases: intended population
  - How extrapolate data from patients in trial to more general population
  - Inclusion of groups previously underrepresented in studies
    - Women, pediatric patients, elderly

Choice of Control

- Necessary in order to determine if drug works (generally phase II/III)
- Different types:
  - Placebo (in right setting) is clearest way to demonstrate efficacy
  - Approved therapy (active control)
    - Superiority or equivalence
  - Different doses of same agent
  - Historical

Placebo-Controlled Trials

- If there is a known effective Rx, some groups have raised concern about use of placebo even if no lasting harm
- Unethical to withhold known effective Rx if irreversible harm
- In some cases, placebo or active agent may be added to standard of care

Non-Inferiority Trials

- Non-inferiority trials attempt to show efficacy by showing a new treatment is as effective as a known effective therapy
- Demonstrate that a new agent is not worse than the control by some narrow margin

Non-Inferiority Trials: Disadvantages

- Assay sensitivity: If active control does not show consistent results, cannot reach firm conclusions
- May require a very large sample size to rule out small degree of inferiority

Choice of Endpoint

- Depends on the phase of development, clinical setting, intended effect of drug
- May be many- range of safety (phase I) and activity/effect (esp. in phase II)
- Generally, for approval an efficacy endpoint should be a clinical benefit or be a validated surrogate that best measures the clinical benefit of interest

Surrogate Markers

- **Used to diagnose disease or evaluate patient response to treatment**
  - **Effect on surrogate marker should reflect equivalent effect on disease or true clinical endpoint of interest**
- Advantages
  - Easier and faster to measure, occurs in more patients, decreased costs of study
- Disadvantages
  - If wrong, may result in overestimation or underestimation of true effect

Confounding Factors

- Bias
- Regression to the mean-
  - phenomenon that occurs when making a second or subsequent measurement only on extreme outliers. 2nd measurement tends to be less extreme than the first
- Imbalance between study arms
- Dropouts
- Multiple endpoints

Evaluation of Efficacy

- Study design
  - Appropriateness of study design for indication
  - Randomized, concurrent control
  - Well-defined selection of subjects
  - Appropriate endpoints
  - Appropriate choice of control group(s)

Final Analysis

- Do the results show that the product is safe under the conditions of use in the proposed labeling?
- Do the results of well-controlled studies provide substantial evidence of effectiveness?